NAFCILLIN SODIUM - nafcillin sodium injection, solution
Sandoz Inc.

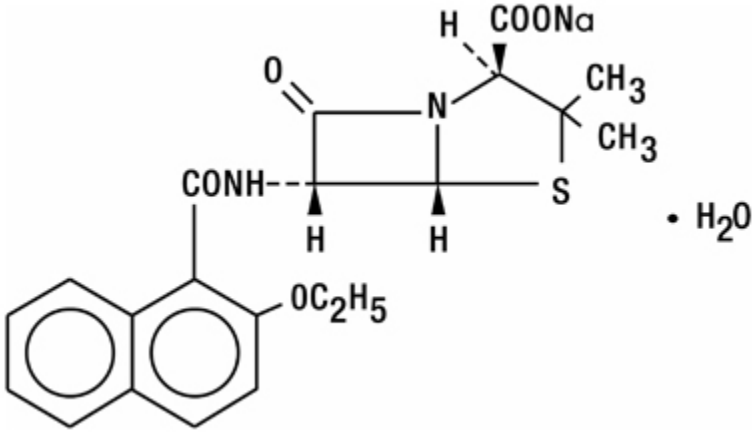
For Intravenous Injection Only

In ADD-Vantage® Drug Delivery System

To reduce the development of drug-resistant bacteria and maintain the effectiveness of nafcillin for injection and other antibacterial drugs, nafcillin for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Nafcillin for injection, USP ADD-Vantage is a sterile, semisynthetic antibiotic substance derived from 6-amino-penicillanic acid intended for intravenous administration only. Each gram of nafcillin contains approximately 2.9 mEq of sodium and is buffered with 40 mg sodium citrate. Nafcillin sodium, $C_{21}H_{21}N_2NaO_5S•H_2O$ molecular weight 454.47, is designated as 4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid, 6-[[(2-ethoxy-1-naphthalenyl) carbonyl] amino]-3,3-dimethyl-7-oxo-monosodium salt, monohydrate, [2*S*-(2α, 5α,6β)] and has the following structural formula:



CLINICAL PHARMACOLOGY

In a study of five healthy adults administered a single 500 mg dose of nafcillin by intravenous injection over seven minutes, the mean plasma concentration of the drug was approximately 30 mcg/mL at 5 minutes after injection. The mean area under the plasma concentration-versus-time curve (AUC) for nafcillin in this study was 18.06 mcg•h/mL.

The serum half-life of nafcillin administered by the intravenous route ranged from 33 to 61 minutes as measured in three separate studies.

In contrast to the other penicillinase-resistant penicillins, only about 30% of nafcillin is excreted as unchanged drug in the urine of normal volunteers, and most within the first six hours. Nafcillin is primarily eliminated by nonrenal routes, namely hepatic inactivation and excretion in the bile.

Nafcillin binds to serum proteins, mainly albumin. The degree of protein binding reported for nafcillin is 89.9 ± 1.5%. Reported values vary with the method of study and the investigator.

The concurrent administration of probenecid with nafcillin increases and prolongs plasma concentrations of nafcillin. Probenecid significantly reduces the total body clearance of nafcillin with renal clearance being decreased to a greater extent than nonrenal clearance.

The penicillinase-resistant penicillins are widely distributed in various body fluids, including bile, pleural, amniotic and synovial fluids. With normal doses insignificant concentrations are found in the aqueous humor of the eye. High nafcillin CSF levels have been obtained in the presence of inflamed meninges.

Renal failure does not appreciably affect the serum half-life of nafcillin; therefore, no modification of the usual nafcillin dosage is necessary in renal failure with or without hemodialysis. Hemodialysis does not accelerate the rate of clearance of nafcillin from the blood.

A study which assessed the effects of cirrhosis and extrahepatic biliary obstruction in man demonstrated that the plasma clearance of nafcillin was significantly decreased in patients with hepatic dysfunction. In these patients with cirrhosis and extrahepatic obstruction, nafcillin excretion in the urine was significantly increased from about 30 to 50% of the administered dose, suggesting that renal disease superimposed on hepatic disease could further decrease nafcillin clearance.

Microbiology

Penicillinase-resistant penicillins exert a bactericidal action against penicillin-susceptible microorganisms during the state of active multiplication. All penicillins inhibit the biosynthesis of the bacterial cell wall.

The drugs in this class are highly resistant to inactivation by staphylococcal penicillinase and are active against penicillinase-producing strains of **Staphylococcus aureus**.

The penicillinase-resistant penicillins are active *in vitro* against a variety of other bacteria.

Susceptibility Tests

Diffusion Techniques
Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure that has been recommended for use with disks to test the susceptibility of microorganisms to nafcillin uses the 1 mcg nafcillin disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for nafcillin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 1 mcg nafcillin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 13	Susceptible (S)
11 – 12	Intermediate (I)
≤ 10	Resistant (R)

A report of “Susceptible” indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **CLINICAL PHARMACOLOGY** section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 1 mcg nafcillin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
S. aureus ATCC 25923	16 – 22

Dilution Techniques
Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[2] (broth, agar, or microdilution) or equivalent with nafcillin powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 2	Susceptible (S)
–	Intermediate (I)
≥4	Resistant (R)

Interpretation should be as stated above for results using diffusion techniques. As with standard diffusion techniques, dilution methods require the use of laboratory control microorganisms. Standard nafcillin powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
S. aureus ATCC 29213	0.12 – 0.5
E. faecalis ATCC 29212	2 – 8

INDICATIONS AND USAGE
Nafcillin is indicated in the treatment of infections caused by penicillinase-producing staphylococci which have demonstrated susceptibility to the drug. Culture and susceptibility tests should be performed initially to determine the causative organism and its susceptibility to the drug (see **CLINICAL PHARMACOLOGY: Susceptibility Tests**).
Nafcillin may be used to initiate therapy in suspected cases of resistant staphylococcal infections prior to the availability of susceptibility test results. Nafcillin should not be used in infections caused by organisms susceptible to penicillin G. If the

susceptibility tests indicate that the infection is due to an organism other than a resistant staphylococcus, therapy should not be continued with Nafcillin.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of nafcillin for injection and other antibacterial drugs, nafcillin for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS
A history of a hypersensitivity (anaphylactic) reaction to any penicillin is a contraindication. Solutions containing dextrose may be contraindicated in patients with known allergies to corn or corn products.

WARNINGS
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH NAFCILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, NAFCILLIN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Nafcillin Injection, USP, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General
Nafcillin should generally not be administered to patients with a history of sensitivity to any penicillin.
Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma. Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy. The use of antibiotics may result in overgrowth of nonsusceptible organisms. If new infections due to bacteria or fungi occur, the drug should be discontinued and appropriate measures taken.
The liver/biliary tract is the primary route of nafcillin clearance. Caution should be exercised when patients with concomitant hepatic insufficiency and renal dysfunction are treated with nafcillin. Serum levels should be measured and the dosage adjusted appropriately to avoid possible neurotoxic reactions associated with very high concentrations (see **DOSAGE AND ADMINISTRATION**).
Prescribing nafcillin for injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients
Patients should be counseled that antibacterial drugs including Nafcillin Injection, USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Nafcillin for Injection, USP is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Nafcillin Injection, USP or other antibacterial drugs in the future. Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Laboratory Tests
Bacteriologic studies to determine the causative organisms and their susceptibility to the penicillinase-resistant penicillins should be performed (see **CLINICAL PHARMACOLOGY: Microbiology**). In the treatment of suspected staphylococcal infections, therapy should be changed to another active agent if culture tests fail to demonstrate the presence of staphylococci.
Periodic assessment of organ system function including renal, hepatic, and hematopoietic should be made during prolonged therapy with nafcillin.
White blood cell and differential cell counts should be obtained prior to initiation of therapy and periodically during therapy with nafcillin.
Periodic urinalysis, blood urea nitrogen, and creatinine determinations should be performed during therapy with nafcillin.
SGOT and SGPT values should be obtained periodically during therapy to monitor for possible liver function abnormalities.

Drug Interactions
Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin and concurrent use of these drugs should be avoided.
Nafcillin in high dosage regimens, i.e., 2 grams every 4 hours, has been reported to decrease the effects of warfarin. When nafcillin and warfarin are used concomitantly, the prothrombin time should be closely monitored and the dose of warfarin adjusted as necessary. This effect may persist for up to 30 days after nafcillin has been discontinued.
Nafcillin when administered concomitantly with cyclosporine has been reported to result in subtherapeutic cyclosporine levels. The nafcillin-cyclosporine interaction was documented in a patient during two separate courses of therapy. When cyclosporine and nafcillin are used concomitantly in organ transplant patients, the cyclosporine levels should be monitored.

Drug/Laboratory Test Interactions
Nafcillin in the urine can cause a false-positive urine reaction for protein when the sulfosalicyclic acid test is used, but not with the dipstick.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been conducted with these drugs. Studies on reproduction (nafcillin) in rats and mice reveal no fetal or maternal abnormalities before conception and continuously through weaning (one generation).

Pregnancy

Teratogenic Effects

Pregnancy Category B
Reproduction studies have been performed in the mouse with oral doses up to 20 times the human dose and orally in the rat at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the rodent fetus due to nafcillin. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, nafcillin should be used during pregnancy only if clearly needed.

Nursing Mothers
Penicillins are excreted in Human milk. Caution should be exercised when penicillins are administered to a nursing woman.

Pediatric Use
(Conventional Vial Use Only) The liver/biliary tract is the principal route of nafcillin elimination. Because of immature hepatic and renal function in pediatric patients, nafcillin excretion may be impaired, with abnormally high serum levels resulting. Serum levels should be monitored and the dosage adjusted appropriately.[1,2] There are no approved pediatric patient dosage regimens for intravenous nafcillin. Safety and effectiveness in pediatric patients have not been established. The potential for toxic effects in pediatric patients from chemicals that may leach from the single dose premixed intravenous preparation in plastic containers has not been determined.

Geriatric Use
Clinical studies of Nafcillin for Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
Nafcillin for Injection contains 76.6 mg (3.33 mEq) of sodium per gram. At the usual recommended doses, patients would receive between 230 and 460 mg/day (10 and 20 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

ADVERSE REACTIONS

Body as a Whole

The reported incidence of allergic reactions to penicillins ranges from 0.7 to 10 percent (see **WARNINGS**). Sensitization is usually the result of treatment but some individuals have had immediate reactions to penicillin when first treated. In such cases, it is thought that the patients may have had prior exposure to the drug via trace amounts present in milk or vaccines.

Two types of allergic reactions to penicillin are noted clinically, immediate and delayed.

Immediate reactions usually occur within 20 minutes of administration and range in severity from urticaria and pruritus to angioneurotic edema, laryngospasm, bronchospasm, hypotension, vascular collapse, and death. Such immediate anaphylactic reactions are very rare (see **WARNINGS**) and usually occur after parenteral therapy but have occurred in patients receiving oral therapy. Another type of immediate reaction, an accelerated reaction, may occur between 20 minutes and 48 hours after administration and may include urticaria, pruritus, and fever. Although laryngeal edema, laryngospasm, and hypotension occasionally occur, fatality is uncommon.

Delayed allergic reactions to penicillin therapy usually occur after 48 hours and sometimes as late as 2 to 4 weeks after initiation of therapy. Manifestations of this type of reaction include serum sickness-like symptoms (i.e., fever, malaise, urticaria, myalgia, arthralgia, abdominal pain) and various skin rashes. Nausea, vomiting, diarrhea, stomatitis, black or hairy tongue, and other symptoms of gastrointestinal irritation may occur, especially during oral penicillin therapy.

Local Reactions

Pain, swelling, inflammation, phlebitis, thrombophlebitis, and occasional skin sloughing at the injection site have occurred with intravenous administration of nafcillin (see **DOSAGE AND ADMINISTRATION**). Severe tissue necrosis with sloughing secondary to subcutaneous extravasation of nafcillin has been reported.

Nervous System Reactions

Neurotoxic reactions similar to those observed with penicillin G could occur with large intravenous or intraventricular doses of nafcillin especially in patients with concomitant hepatic insufficiency and renal dysfunction (see **PRECAUTIONS**).

Urogenital Reactions

Renal tubular damage and interstitial nephritis have been associated infrequently with the administration of nafcillin. Manifestations of this reaction may include rash, fever, eosinophilia, hematuria, proteinuria, and renal insufficiency. Gastrointestinal Reactions

Pseudomembranous colitis has been reported with the use of nafcillin. The onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see **WARNINGS**).

Metabolic Reactions

Agranulocytosis, neutropenia, and bone marrow depression have been associated with the use of nafcillin.

OVERDOSAGE

Neurotoxic reactions similar to those observed with penicillin G may arise with intravenous doses of nafcillin especially in patients with concomitant hepatic insufficiency and renal dysfunction (see **PRECAUTIONS**).

In the case of overdosage, discontinue nafcillin, treat symptomatically and institute supportive measures as required. Hemodialysis does not increase the rate of clearance of nafcillin from the blood.

DOSAGE AND ADMINISTRATION

Bacteriologic studies to determine the causative organisms and their susceptibility to nafcillin should always be performed. Duration of therapy varies with the type and severity of infection as well as the overall condition of the patient, therefore it should be determined by the clinical and bacteriological response of the patient. In severe staphylococcal infections, therapy with nafcillin should be continued for at least 14 days. Therapy should be continued for at least 48 hours after the patient has become afebrile, asymptomatic, and cultures are negative. The treatment of endocarditis and osteomyelitis may require a longer term of therapy. Nafcillin-therapy is generally limited to those infections where very high serum levels of nafcillin are necessary.

Oral therapy with the penicillinase-resistant penicillins may be used to follow-up the previous use of a parenteral agent as soon as the clinical condition warrants.

Recommended Dosages for Nafcillin for Injection, USP in ADD-Vantage Drug Delivery System:

Adults: 3 to 6 g per 24-hour period.

Directions for Use

Nafcillin For Injection vials in the ADD-Vantage Drug Delivery System are for IV use only and are to be used with ADD-Vantage diluent containers of 0.9% Sodium Chloride Injection, USP 50 mL and 100 mL, or 5% Dextrose Injection, USP, 50 mL and 100 mL. Reconstitute ADD-Vantage vials as directed in the **Instructions for Use** section.

Only 0.9% Sodium Chloride Injection, USP, and 5% Dextrose Injection, USP are available for use in the ADD-Vantage Delivery System for intravenous infusion of nafcillin sodium. The drug concentration and the rate and volume of the infusion should be adjusted so that the total dose of nafcillin is administered before the drug loses its stability in the solution in use.
There is no clinical experience available on the use of this agent in neonates or infants for this route of administration.
This route of administration should be used for relatively short-term therapy (24 to 48 hours) because of the occasional occurrence of thrombophlebitis particularly in elderly patients.
If another agent is used in conjunction with nafcillin therapy, it should not be physically mixed with nafcillin but should be administered separately.

Instructions for Use
To Open Diluent Container:
Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.
To Assemble Vial and Flexible Diluent Container:
(Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:
   a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (see **Figure 1**) then pull straight up to remove the cap (see **Figure 2**). NOTE: Do not access vial with syringe.

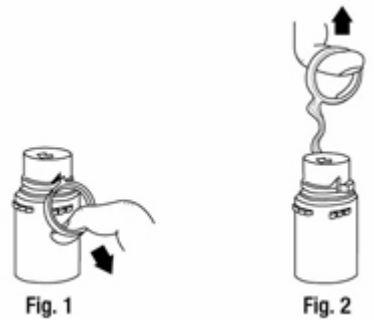


Fig. 1

Fig. 2

   b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover (see **Figure 3**).

2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately 1/2 turn (180°) after the first audible click (see **Figure 4**). The clicking sound does not assure a seal; the vial must be turned as far as it will go. NOTE: Once vial is seated, do not attempt to remove (see **Figure 4**).

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.

4. Label appropriately.

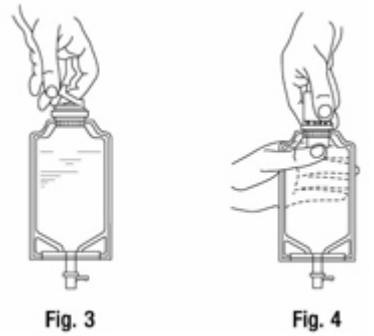


Fig. 3

Fig. 4

To Prepare Admixture:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.

2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container (see **Figure 5**).

3. Pull the inner cap from the drug vial (see Figure 6). Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.

4. Mix container contents thoroughly and use within the specified time.

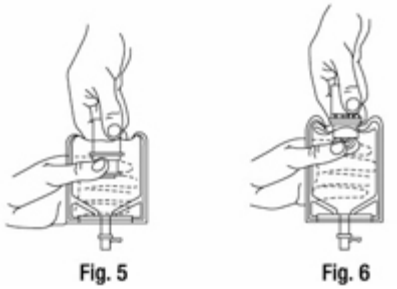


Fig. 5 Fig. 6

Preparation for Administration:
(Use Asceptic Technique)

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.
At concentrations ranging from 10 to 40 mg/mL in either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP nafcillin sodium will have utility times of 24 hours at room temperature (25°C).

HOW SUPPLIED
Nafcillin for Injection, USP ADD-Vantage for IV Injection. Nafcillin sodium equivalent to 1 gram or 2 grams nafcillin per vial.
NDC 0781-3128-92, 1 gram ADD-Vantage Vial, packed in 10s
NDC 0781-3129-92, 2 gram ADD-Vantage Vial, packed in 10s
Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature).
®ADD-Vantage is a trademark of Hospira Inc.

REFERENCES

1. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests*, Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1 NCCLS, Wayne, PA, January, 2000.
2. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2 NCCLS, Wayne, PA, January, 2000.

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